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(21) International Application Number: PCT/US85/00938 (22) International Filing Date: 20 May 1985 (20.05.85) (31) Priority Application Number: 621,392 (32) Priority Date: 18 June 1984 (18.06.84) (33) Priority Country: US (71) Applicant: UNIVERSITY OF MISSOURI [US/US]; 215 Columbia Hall, Columbia, MO 65211 (US). (72) Inventors: TWARDOWSKI, Zbylut, J. ; 304 Devine Ct., Columbia, MO 65203 (US). NOLPH, Karl, D. ; 908 Hickory Hill Drive, Columbia, MO 65203 (US). (74) Agents: RYAN, Daniel, D. et al.; One Baxter Parkway, Deerfield, IL 60015 (US).		(81) Designated States: AT (European patent), BE (Euro- pean patent), CH (European patent), DE (European patent), DK, FR (European patent), GB (European patent), IT (European patent), JP, LU (European pa- tent), NL (European patent), SE (European patent). Published. <i>With international search report.</i>
(54) Title: DIALYSIS SOLUTIONS CONTAINING CROSS-LINKED GELATIN (57) Abstract Peritoneal dialysis solution may have an osmotic agent as a partial or complete substitute to the conventional dex- trose. The osmotic agent is gelatin chemically cross-linked to suppress gelation.		

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DIALYSIS SOLUTIONS CONTAINING CROSS-LINKED GELATIN
TECHNICAL FIELD AND PRIOR ART

In Kartinos et al., U.S. patent 4,339,433, polymeric osmotic agents are proposed for use in peritoneal dialysis solution as an alternative to dextrose.

5 The dextrose in the conventional peritoneal dialysis solution is provided to cause ultrafiltration to take place by osmotic principles from the blood through the peritoneum of a patient into the dialysis solution in the peritoneal cavity, to cause removal of water from the dialysis patient.

10 While dextrose is an effective material and virtually the only osmotic agent used in commercially available peritoneal dialysis solution at the present time, it has certain drawbacks. First, a great deal of dextrose passes through the peritoneum into the patient's bloodstream during peritoneal
15 dillysis. While this does provide carbohydrate nutrition, difficulties can be encountered by some groups of patients, particularly diabetic patients and certain other patients who have a tendency to develop high serum lipids in the presence of such large amounts of glucose.

20 Since end stage renal disease patients, whose lives are being maintained by dialysis, must undergo a certain amount of ultrafiltration every day to remove water from their circulatory systems, it is not practical simply to reduce the amount of dextrose in the peritoneal dialysis solution. The
25 ultrafiltration that it provides is mandatory in most cases.

 Accordingly, in the Kartinos patent cited above, alternate materials to dextrose were proposed; specifically, a predominantly sodium salt of a reaction product of gelatin and a dicarboxylic acid or its anhydride, to produce a polyanionic
30 protein material having pendant carboxyl groups. The gelatin material makes use of the polyanionic characteristic provided by

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the pendant carboxyl groups on the material to provide osmotic characteristics to the solution.

In accordance with this invention, new gelatin-based osmotic agents for peritoneal dialysis solutions are proposed. Some of
5 these agents appear to have reduced immunogenicity, rendering them highly desirable for use in peritoneal dialysis solution. The new osmotic agents of this invention, being of relatively high molecular weight, pass only slowly through the peritoneum with the result that peritoneal dialysis solutions containing
10 them can retain their capability for ultrafiltration over many hours of dwell in the peritoneal cavity, a period of time which is substantially longer than the corresponding time for glucose-based peritoneal dialysis solutions.

Description of the Invention

15 In this invention a peritoneal dialysis solution is provided having an osmolarity which is capable of permitting safe diffusion exchange across the peritoneum after infusion into the peritoneal cavity of the patient. In accordance with this invention, the peritoneal dialysis solution contains gelatin
20 which is cross-linked to suppress gelation. The peritoneal dialysis solution is at a physiological pH to cause such gelatin to assume polyanionic characteristics, there being sufficient physiological cations present, predominantly sodium, to permit the anionic gelatin to be at such pH. The gelatin is typically
25 essentially free of synthetically added pendant ionizable groups such as carboxyl groups.

It is generally desirable for the peritoneal dialysis solution of this invention to be of at least pH 6 with a typical upper limit being pH 7.5 or 8.0. However, the pH may be as low
30 as 5.2 or 5.5, as may be necessary when dextrose is included in the solution.

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Gelatins which are cross-linked in a manner to suppress gelation are known and commercially available. For example, Haemacel is the trademark of a product of Farbwerke Hoechst A.G. of Frankfurt-Hoechst, West Germany. It is the reaction product of gelatin with an aliphatic diisocyanate, for example examethylene diisocyanate, having a mean molecular weight of 30,000-35,000. For further description, see the article entitled "Chemistry and Physicochemical Characterizations of Gelatin Plasma Substitutes" by H.H. Schöne from Modified
5 Gelatins as Plasma Substitutes; Bibl. haemat., No. 33, pp. 78-80, (Karger, Basel/New York, 1969). The material has been conventionally used as a blood expander for intravenous administration.

Another material which may be used in this invention is sold
15 by Biotest A.G. under the trademark Gelifundol. It is a form of gelatin which is cross-linked with dialdehyde glyoxal.

It has been found that such cross-linked gelatins substantially lack the capability to gel at room temperature and above. They tend to have an isoelectric point at a pH below 5. Accordingly, when the pH is above 5 and preferably 6 to 7.5, the cross-linked gelatins, and particularly those described above, assume an anionic characteristic. Sufficient physiological cations will be provided to the dialysis solution to cause the anionic gelatin to assume a salt form. The primary cation used
20 is typically sodium, although other physiological cations such as potassium, calcium, and/or magnesium may be present as desired along with the sodium. The selection and concentrations of salts for providing said cations is a routine matter for those skilled in the art.

30 As a result of this, the high molecular weight gelatin exhibits increased osmotic effect because of the sodium and other cations that are attracted to the anionic gelatin, while at the same time gelation of the material is suppressed. As a result of this, when placed in the peritoneal cavity as part of

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the peritoneal dialysis solution, the large gelatin polyanions and their associated cations exhibit a relatively long lasting osmotic effect since the gelatin molecules pass only very slowly through the peritoneum into the blood stream of the patient.

- 5 Accordingly, the associated cations are likewise prevented from migration by their electrostatic attraction to the gelatin.

The resulting long-lasting osmotic effect permits ultrafiltration to take place throughout most or all of the dwell period that the peritoneal dialysis solution resides in
10 the peritoneal cavity of the patient, typically a period of 4 to 10 hours. As a result of this, reduced dextrose concentrations can be used in the peritoneal dialysis solution, or not at all in some circumstances. However it may be desired for dextrose to be present in reduced quantities to provide an initial surge
15 of ultrafiltration, and also to provide carbohydrate nutrition to the patient.

Other physiological materials, as may be desired, may be placed in the peritoneal dialysis solution of this invention along with the cross-linked gelatin and appropriate electrolyte
20 salts such as sodium chloride, magnesium chloride, sodium acetate, sodium lactate or potassium chloride. As stated above, dextrose may be added to the solution of this invention, and any other known additive for peritoneal dialysis solution may be present as well.

25

EXAMPLE 1

Nonuremic Sprague Dawley rats weighing 310-390 g. were anesthetized by injection of pentobarbital sodium. A silicone catheter without cuff was inserted into the peritoneal cavity through a midline incision in the abdomen below the sternum.
30 The interior end of the catheter was positioned in the inferior right quadrant of the peritoneal cavity.

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Peritoneal dialysis solution was prewarmed to 37°C, and 20 ml. was administered to each rat over 1 minute of time. Thereafter, the peritoneal dialysis solution was immediately drained in order to determine the undrainable peritoneal solution volume retained in the peritoneal cavity. Then the same aliquot of solution that was drained was reinfused.

Thereafter, at hourly intervals, the peritoneal dialysis solution was drained again, and the volume measured, followed by reinfusion of the same volume of solution until the end of the experiment.

Ultrafiltration volumes as recorded here are the undrainable volume plus the apparent ultrafiltration volumes at each dwell time.

A. A first hemodialysis solution used in the above experiment was of the following formulation:

Hemaccel® cross-linked gelatin-5.5 weight percent

Sodium 147.6 meq./l.

Potassium 4.3 meq./l.

Magnesium 0.59 meq./l.

Calcium 4.79 meq./l.

Chlorine 108 meq./l.

Osmolarity of this solution was 290 milliosmols/kilogram.

The diffusable free electrolytes of the above solution as determined by the Gibbs Donan distribution ratio was as follows:

Sodium 141.1 meq./l.

Potassium 4.1 meq./l.

Magnesium 0.146 meq./l.

Calcium 3.54 meq./l.

Chlorine 111 meq./l.

Osmolarity 272 milliosmols/kilogram.

The experimental results with respect to ultrafiltration for the above solution was as follows:

After 1 hr. of dwell, ultrafiltration was 2.9 ml. \pm 0.4 ml.
After 3 hrs. ultrafiltration was 6.5 ml. \pm 0.5 ml.
5 After 4 hrs. of dwell, ultrafiltration was 7 ml. \pm 0.5 ml.
After 6 hrs. of dwell, ultrafiltration was 6.7 ml. \pm 0.5 ml.
ml.

The following data was determined from 4 rats.

B. The above described experiment was repeated using
10 peritoneal dialysis solution made of the following formulation:

Hemaccel® cross-linked gelatin-10 weight percent
Sodium 149.3 meq./liter
Potassium 4.5 meq./liter
Magnesium 0.64 meq./liter
15 Calcium 5.23 meq./liter
Chlorine 105 meq./liter
Osmolarity 298 milliosmols/kilogram.

The diffusable electrolyte concentrations in accordance with the Gibbs-Donan distribution ratio were substantially
20 identical to the diffusable electrolytes of the previous peritoneal dialysis solution formulation.

Ultrafiltration data from 4 rats tested was as follows:

At 1 hr. of dwell, ultrafiltration was 2.0 ml. \pm 0.2 ml.
At 3 hrs. of dwell, ultrafiltration was 4.6 ml. \pm 0.9 ml.
25 At 4 hrs. of dwell, ultrafiltration was 8.6 ml. \pm 1.0 ml.
At 5 hrs. of dwell, ultrafiltration was 10.6 ml. \pm 0.9 ml.
At 6 hrs. of dwell, ultrafiltration was 11.6 ml. \pm 0.9 ml.

It can be seen that the peritoneal dialysis solutions of this invention exhibit long-term ultrafiltration permitting a relatively steady ultrafiltration over periods of time which may approximate the entire dwell period of a peritoneal dialysis
5 procedure. This can be accomplished in the absence of dextrose, if desired, so that peritoneal dialysis solutions of this invention may exhibit great flexibility of use and benefit to patients who have difficulty tolerating the dextrose contents of the presently conventional peritoneal dialysis solutions.

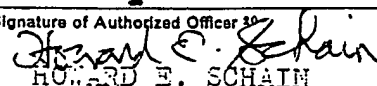
10 The above has been offered for illustrative purposes only and is not intended to limit the scope of the invention of this application, which is as defined in the claims below.

WHAT IS CLAIMED IS:

1. In a peritoneal dialysis solution having an osmolarity capable of permitting safe diffusion exchange across the peritoneum after infusion into the peritoneal cavity of the patient, the improvement comprising:
 - 5 Said solution containing gelatin which is chemically cross-linked to suppress gelation, said solution having a pH whereby said cross-linked gelatin exhibits an anionic character, there been present sufficient physiological cations such as sodium to counterbalance the anionic charge of said gelatin.
- 10 2. The peritoneal dialysis solution of claim 1 in which said cross-linked gelatin is the reaction product of gelatin and an aliphatic diisocyanate.
- 15 3. The peritoneal dialysis solution of claim 1 in which said cross-linked gelatin is the reaction product of gelatin and dialdehyde glyoxal.
4. The peritoneal dialysis solution of claim 1 which has a pH of.
- 20 5. The peritoneal dialysis solution of claim 1 which contains dextrose as an added osmotic agent.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US85/00938

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ³		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC ³ A61K 37/12, 37/18; C09H 7/00; C08L 89/06		
U.S. CL. 260/117; 514/21		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
Classification System	Classification Symbols	
U.S.	260/117; 514/21	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category [*]	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
A	CA, A, 546,929 PUBLISHED 01 OCTOBER 1957 TOURTELLOTTE ET AL	1-5
X	US, A, 3,057,782 LINDNER ET AL PUBLISHED 09 OCTOBER 1962	1-5
Y	US, A, 4,339,433 KARTINOS ET AL PUBLISHED 13 JULY 1982	1-5
Y	<u>MODIFIED GELATINS as PLASMA SUBSTITUTES;</u> Bibl. haemat. No. 33 (KARGER, BASEL/NEW YORK 1969) pp. 55-125.	1-5
<p>[*] Special categories of cited documents: ¹⁵</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search ¹	Date of Mailing of this International Search Report ²	
02 JULY 1985	16 JUL 1985	
International Searching Authority ¹	Signature of Authorized Officer ¹⁹	
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